ORA LABORATORY MANUAL

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Division of Field Science

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Section 6 RESEARCH Section 6

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6.1 Introduction

As the regulatory agency designated to maintain the safety of the nation's foods, drugs, biologics, medical devices, and radiological products, FDA has broad responsibilities to protect the public health. ORA has developed a research program which enables our field laboratories to incorporate new technologies into analytical techniques assessing adulteration and manufacturing problems in the broad spectrum of products FDA regulates.

The field scientific talent is highly varied and complex. So, in addition to the direct application of FDA research results, the research experience enables ORA scientists to maintain the scientific expertise necessary to make sound regulatory decisions.

A block of research time is set aside for this research program each year. The Regional Food and Drug Directors assign a specific number of FTEs to each laboratory based on past research accomplishments, laboratory expertise, and agency need in specialty and program areas. Annually, Laboratory Directors develop a research plan commensurate with their resource allotment.

Generally, the number of FTEs assigned to the laboratories remains the same from year to year. Laboratory Directors manage the research time throughout the year; redirecting the hours towards the highest priority work, and allowing for the introduction of a new research project as needs arise.

The research process has been redesigned to increase flexibility and timely planning of quality research projects that benefit the agency. Planning begins in the laboratories. Analysts develop Research Concept Papers describing potential projects based upon existing and future regulatory needs. The concept papers are submitted to the Research and Technology Transfer Committee (RTTC) for preliminary review. RTTC cleared concept papers are further developed into Research Project Papers. Once project papers are completed, they are submitted to the RTTC for a scientific and technical review. Interaction with research analysts may be needed during the process. Once projects are finalized, research begins as soon as the laboratory research plan allows.

Laboratory management, analysts, and Science Advisors have an important role in managing the research program. Throughout the year, research progress and accomplishments should be

monitored and adjustments made to react to emerging research needs as they arise. Laboratories are expected to fully plan and accomplish their assigned research time.

6.2 Purpose

The purpose of this section is to provide guidance on development, submission, and review of ORA method development and technology transfer research. In addition, the process will assure all projects are of the highest quality, meet regulatory needs, accomplish their intended purpose, include validation where appropriate, and become successful methods.

While enhancing the creative skills of talented individuals in ORA Laboratories, the ORA research program is designed to satisfy the need for regulatory analytical methods meeting current and anticipated public health program needs and agency priorities.

6.3 Background

This LPM section describes the process beginning with FY2005 planning. The historical research process (Field Management Directive 143) can be found in Volume V of the ORA Laboratory Manual, under Archives Files, Section 1, Division of Field Science.

6.3.1 Research Goals

The goals of the Research Program are to:

- provide opportunities for ORA scientists to develop analytical methodologies, to support the regulatory and public health protection mission of FDA;
- enhance the ability of ORA staff to transfer the products of our research to daily operations; and
- develop the knowledge, skills, and abilities of ORA staff analysts.

To achieve these goals ORA management is:

- supportive of practical research that meets current and anticipated Agency needs in the context of ORA's mission in FDA;
- sensitive to improving the overall quality of research projects including proper assessment of the significance, probability of success, and ultimate value of the research;

- cognizant of tangible and intangible benefits that result from research projects;
- supportive of the critical role Science Advisors play in the implementation and execution of research; and
- dedicated to completion of research projects from the point of application through to collaboration and publication.

6.3.2 Role of Field Laboratories

Analytical research in ORA laboratories is designed to mesh with the purpose of research for the Agency as a whole. On the basis of input from the field laboratories, research centers, and headquarters Centers, ORA Laboratory Directors with their Science Advisors and the RTTC develop an ongoing research plan.

The plan is directed toward meeting FDA priority goals and objectives such as:

- developing analytical methods and expertise to solve continuing, new, or emerging regulatory problems;
- upgrading present methods to use improved instrumentation or technology; and
- validating methods for official status by AOAC International (AOAC) or United States Pharmacopeial Convention, Inc (USP).

6.3.3 Types of Research

6.3.3.1 Planned Research

Planned research is designed to handle regulatory program-oriented research problems. The research can be conceived by headquarters units, district offices, and/or Science Advisors. Laboratory Directors determine how their assigned research FTEs will be used. These resources are allocated in the annual ORA work plan. The results of this research may directly affect Center regulatory program development.

6.3.3.2 District Discretionary Research

In each district laboratory's annual work plan, a number of hours of unplanned research time per operational scientist are included to handle problems that arise during planned sample analysis or for research not covered by other research programs. The policies and procedures applicable to this research are controlled by local management.

6.3.3.3 Compliance Program Directed Research

Research operations mandated in compliance programs are planned in the Centers and conducted by ORA. The ORA researcher assigned to the project has latitude to plan activities to explore and solve the problem, but the Center and ORA *through DFS*, define the parameters for the scope of the study.

6.3.3.4 Science Advisor Research Associate Program

The Science Advisor Research Associate Program (SARAP) was initiated in 1973 in order to provide field professionals with an opportunity for uninterrupted training and research involvement. The program allows researchers to become or remain current in advancing scientific and technical skills.

The purpose of the SARAP program is:

- to permit and encourage scientifically competent field employees to develop themselves for research and specialty positions through a planned staff development program;
- to upgrade the quality and status of field scientific research development and investigations;
- to develop a cadre of well-trained field scientists and investigators capable of meeting the challenges posed by the demand for more complex method development and investigations; and
- to introduce new scientific techniques and capability into our field laboratories.

SARAP research can be conducted at a local college or university, FDA laboratory, or a combination of both under the direction of laboratory management, and/or Science Advisor, or other academic professor.

Up to one full FTE of research time may be granted to the SARAP associate. An analyst interested in participating in a SARAP project would submit a concept paper to the Laboratory Director. SARAP time would come from the research FTEs assigned to the laboratory. The Associate Commissioner for Regulatory Affairs approves all the necessary funding for SARAP research. (Please refer to SARAP guidelines at DFS).

6.3.3.5 Cooperative Research and Development Agreement

The Federal Technology Transfer Act of 1986, (FTTA), authorizes government agencies to enter into collaborations with the private sector, academic institutions, and other organizations. The mechanism used is known as the Cooperative Research and Development Agreement (CRADA).

A CRADA is used to formalize a specific collaborative project which may involve research leading to new inventions or further development of existing government or non-government inventions in fulfillment of FDA missions. The primary purpose is to transfer the technology/intellectual property to the commercial marketplace. The terms of a CRADA, which are negotiated by FDA and the collaborator, may address patent rights and licensing matters as well as the collaborative research project.

The FTTA provides that the government inventor(s) responsible for developing the technology receive(s) a share of any income/royalties which are paid to FDA as a result of its commercialization. However the Act should be implemented within the context of existing conflict of interest laws and DHHS and FDA regulations regarding employee conduct. The purpose of the Act is to achieve greater utilization and commercialization of technologies and inventions developed in government laboratories and through collaborative research projects. Within this context, FDA Centers and ORA are encouraged to use CRADA when it is an appropriate means for accomplishing a collaborative research activity.

A CRADA is appropriate when:

- the FDA scientist/collaborator is expected to make a significant intellectual and material contribution to the research activity/collaboration;
- an invention is a reasonably expected product of the collaboration; or
- the collaboration is intended to further develop an existing technology or patented invention which may then be commercialized.

A CRADA is not intended to be a general funding mechanism. CRADA-derived funds are to be used for costs associated with the project specified in the CRADA. Laboratories must be prepared to address the impact to ongoing research if a CRADA and related financial support is terminated unexpectedly.

The sole purpose of a CRADA cannot be to support post-doctoral fellows and/or technicians, to obtain funds, or to purchase equipment and/or supplies. Conversely, the sole justification of a CRADA cannot be for an FDA laboratory to conduct research or tests for the collaborator.

When initiating a CRADA, the FDA principal investigator/project officer should certify on the "Conflict of Interest and Fair Access Statement" that he/she:

- has read the applicable conflict of interest laws and regulations, and

- either indicated that none of the situations apply by checking "No," or identified any situation which could give the appearance of a conflict of interest.

The FDA's Ethics and Personnel Security Branch will use the information provided by the principal investigator and Center management to determine what, if any, conflicts exist and recommend the necessary action for resolution.

More information can be obtained from http://eric.fda.gov under Acquisition and Grants and under Technology Transfer.

Time allotted to a CRADA project can be taken from a laboratory's discretionary time, planned research allotment, or by agreement with a Center to use other compliance program planned time.

6.3.3.6 Field Research Center Research

In the early 1980s, field research centers were established in several ORA laboratories to focus research efforts in support of a variety of program areas. Three field research centers remain: Seafood Products Research Center (Seattle), Animal Drugs Research Center (Denver), and Total Diet & Pesticide Research Center (Kansas City). In addition, the Atlanta Center for Nutrient Analysis performs similar functions in part. The field research centers provide complex analytical support to field laboratories and the Centers, conducting research on current methodology, developing and refining new rapid chemical and biological methodology, conducting and participating in collaborative studies and validation trials of analytical methods, and providing expert technical scientific assistance and consultative services. Research programs are developed independent of the field laboratory process described in this chapter. Projects are defined through meetings with the associated Centers and DFS, or by a call for projects and needs to all field laboratories.

6.4 Roles and Responsibilities

6.4.1 Associate Commissioner for Regulatory Affairs (ACRA)

The Associate Commissioner for Regulatory Affairs (ACRA) is the final approval authority for Science Advisors Research Associate Program (SARAP) projects and provides funding, if available, for execution of the research.

6.4.2 Office of Regional Operations (ORO)

The Director of the Office of Regional Operations (ORO), is the recommending official to the ACRA for approval of SARAP projects. The Director of ORO shares responsibility for promoting and supporting a strong ORA research program along with determining ORA research goals.

6.4.3 Science Branch and Laboratory Directors

Direction and management of the ORA research resources resides at the local laboratory management level. Laboratory management is responsible for developing and executing their laboratory's research program. This includes: developing and selecting the most significant research projects, providing funding, and assuring that work plan resources are fully planned and executed. Timely planning, direction, and accomplishment of research projects are crucial. Laboratory Directors rely on supervisors, senior laboratory staff, and Science Advisors.

Laboratory management must establish an environment where there is vigorous growth, development, and accomplishment of projects within the laboratories. Recognition that is commensurate with the level of contribution to the regulatory mission of ORA and FDA by scientists who successfully complete research projects is an important aspect of a successful program.

Laboratory Directors coordinate collaborations and method validation by communicating with the Center regarding criteria for validation.

6.4.4 Science Advisors

Science Advisors aid Laboratory Directors in the management of the research process at the local level, including being familiar with the research timelines and assuring that deadlines are met. They will report status on progress of individual projects to their Laboratory Directors and DFS and make recommendations for improving the research. They provide guidance on development of concept and research project papers, and assist in the conduct, evaluation, and presentation of research. They promote interaction and collaborations with their respective universities and other science advisors where appropriate.

6.4.5 ORA Analysts

ORA analysts adhere to the highest standards of intellectual honesty and ethical standards in formulating, conducting, and presenting research. They work with colleagues, supervisors and Science Advisors to develop and submit research concepts and further develop approved concept papers into research proposals. Naturally, their major contribution is the performance and completion of the research.

6.4.6 Research and Technology Transfer Committee (RTTC)

Positions on the Research and Technology Transfer Committee (RTTC) are held for two years and can be renewed. The Chair and DFS Science Advisor are permanent. The Committee Chair recommends replacements with concurrence of the Director of ORO.

The RTTC reviews and approves concept papers. It conducts a scientific and technical review of research projects. Reviewers consider mission relevance and quality of the science, as well as written project quality and completeness. The RTTC determines support of continuations or modifications of projects prior to their proceeding. Technical comments and guidance are provided to analysts to finalize the projects.

The RTTC can propose research to meet emerging or immediate needs that arise outside the normal review process and recommend collaborations.

6.4.7 Division of Field Science (DFS)

The Division of Field Science (DFS) participates in all meetings and deliberations of the RTTC and develops and implements research guidelines. DFS issues the call for concept papers, designates in-depth reviewers for research projects, assigns Research Project Numbers (RPN) and compiles and maintains the approved project list. DFS works with the RTTC and Science Advisors to guide and assist Laboratory Directors and analysts with the research process. The Director of DFS is the recommending official for field laboratory research programs. DFS monitors the various steps in the process, issues requests, and receives concept papers, project papers, progress reports, etc.

6.4.8 Science Advisor Working Group (SAWG)

The Science Advisor Working Group (SAWG) reviews and prepares an annual impact report of both research achievements and areas of concern for future research planning. Periodic follow-up reports on research include regulatory impact, publications, presentations, collaborative studies, adoption as official methods by additional field and headquarters laboratories, inclusion in compliance programs, etc.

6.5 ORA Research Process

6.5.1 Laboratory Research Program

Each ORA laboratory will be required to have an ongoing research program commensurate with their research time allotment. In advance of each fiscal year, DFS will call for the program plan.

The plan will be developed from projects that are reviewed through the Research Planning Process outlined in this ORA Laboratory Manual and Field Management Directive 143 (FMD 143). Projects can be added and deleted from the annual plan as time and priorities dictate. Characteristics of a good program are that it is mission related and does not duplicate research work being done elsewhere.

6.5.2 Basic Steps of the Process

The basic steps in the Research Planning Process for each research project are:

- Development of a concept paper expressing the area to be researched, its relevance, and the scientific approach.
- Approval of the concept by the RTTC.
- Development of a project paper with details of the mission relevance, scientific approach, and expected outcomes.
- In-depth review by the RTTC and approval or redirection.
- Allotment of time and resources to accomplish the research in the Laboratory Research Plan by the Laboratory Director.
- Performance of the research.
- Write-up of the results and presentation for publication.

The details and timing of the research process are fully explained in the call notice and FMD 143.

6.5.3 Management of Research Program

Laboratory Directors are responsible for the development and execution of their laboratory's research program. To facilitate the management of the program, the Laboratory Directors are encouraged to use their Science Advisors for the development of research ideas, monitoring progress of projects, and providing research quality oversight. Science Advisors are expected to maintain communication with the researching analyst, laboratory management, and DFS in particular providing status and progress on individual projects. Each laboratory should coordinate with other ORA laboratories and Center scientists. This may result in a collaborative approach to resolve certain problems.

ORA research activities are coordinated by DFS. The Division's responsibility to the research planning process is to provide formalized policies and procedures that facilitate the planning, execution, review, and evaluation of ORA research programs. The immediate management of specific research projects is the responsibility of local management.

DFS has ongoing contact with the Centers that could identify research possibilities at any time. In addition, DFS will make formal contact with the Centers twice a year to identify any research needs that they would like to have addressed by field scientists. Their responses are distributed to the field laboratories and Science Advisors for consideration as planned research projects.

In addition to Center input, Laboratory Directors, analysts and Science Advisors are strongly encouraged to identify research needs via regular meetings and discussions. Science Advisors may generate ideas from the monthly Science Advisor conference calls. Once a research need has been identified, the next step is to develop it into a research concept paper.

DFS issues calls to field laboratories for Research Concept Papers for workplan, or Science Advisor Research Associate Program (SARAP) research, in advance of each RTTC meeting. Starting with FY05, the concept paper can be submitted at any time to be reviewed by the RTTC at the next available quarterly meeting. However, timing should be such that the laboratories each have a fully planned research program in progress.

Concept papers should include mission relevance and regulatory significance to support the project. With the guidance of their Science Advisors, analysts prepare and submit concept papers to their Laboratory Directors. The Research Concept Paper form can be found in FMD 143.

Laboratory Directors send to DFS all concept papers they have determined to be appropriate research work, that fall within their allotted research FTEs and can be supported with laboratory funds. No additional funding is available for regular workplan research. Past SARAP projects have received funding from the ACRA when funds were available.

6.5.4 Evaluation of Research Concept Papers

The RTTC reviews concept papers for mission relevance, scientific soundness, and quality of write-up. The Centers may be asked for comments on the proposed research. The results of the review are communicated to the Laboratory Director and local Science Advisor for appropriate follow up action. The RTTC will meet quarterly, through teleconference, to evaluate any pending concept papers. In the event a project needs immediate review, DFS will identify an appropriate available RTTC member to perform this review.

6.5.5 Development and Evaluation of Research Project Papers

Following the concept paper review and acceptance by the RTTC, Laboratory Directors direct analyst(s) to further develop the concept papers into full Research Project Papers.- Completed project papers are forwarded to DFS for a scientific and technical review by the RTTC before the project can start. Submission of a Research Project Paper is a commitment on the part of the Laboratory Director to support and accomplish the research project. It is the responsibility of the Laboratory Director to have ready adequate projects to insert into their overall research plan as time and funding permit.

Research Project Papers are to be prepared using the Research Project Paper form in FMD 143 and submitted following the prescribed procedure. Project papers must address the needs identified in the previously approved Research Concept Paper unless accompanied by a substantial justification regarding the revised research concept.

DFS issues a call in advance of each RTTC research planning meeting, with due dates for submitting full project papers from the RTTC supported concepts. Center contacts should be identified and communication established if the researcher feels it is needed. At this time projects may also be recommended for collaboration or publication.

DFS assigns an in-depth reviewer on the RTTC to each project paper. The RTTC meets to discuss and review the projects. Based upon the committee discussion, feedback is provided to the laboratory, science advisor, and analyst to redirect and/or finalize the project. When the project review becomes finalized a Research Project Number (RPN) number is assigned by DFS for entering time into FACTS. The project commences according to the laboratory's research plan.

6.5.6 Laboratory Research Plan

Each laboratory is responsible for developing a Research Plan that accounts for the allotted research hours in a fiscal year. The plan will be expressed in the Research Summary Spreadsheet maintained in each laboratory and updated to DFS quarterly. The laboratory is given a number of fixed research hours with each year's work plan. With timely submission of Research Concept Papers and Research Project Papers, the Laboratory Director can insert approved research projects into the plan as needed. Flexibility is key to successful execution of the plan. With quarterly meetings of the RTTC to review concept and project papers, approved projects can be added to the plan at any time throughout the year and can overlap years if needed.

Laboratory Directors will be expected to report on their successful management and accomplishment of their research plan with performance reviews. Successful past research accomplishment will be one of the factors considered when work planning is adjusted as programs increase or decrease.

6.6 Reporting Requirements

6.6.1 Research Summary Spreadsheet

On a quarterly basis, each laboratory is required to submit a research summary spreadsheet which indicates the status of each research project, adding new potential projects when concept papers are submitted. The Science Advisors should be relied upon to develop and submit these reports through the Laboratory Directors. DFS will update information from the quarterly spreadsheets into a main spreadsheet that will be available on the DFS Webpage. The compilation of all the Research Summary Spreadsheets from all the ORA laboratories will be the Research Technical Plan. The format for this report in on the DFS Webpage and is attached to FMD 143.

6.6.2 Research Progress Reports and Impact Reports

In addition to the quarterly spreadsheet updates, greater detailed progress reports describe the specifics on research progress. When approximately half of the allotted time is expended on a project, but no more that two-thirds of the time or within a year of initiation (whichever is less), a progress report is prepared and submitted to DFS. This is required for projects of 500 hours or more, or a project of lesser time being executed over a period of one year or more. At completion of a research project, or when a significant impact is realized, an Impact Report will be prepared by the analyst and Science Advisor and submitted to DFS. All of the forms are posted on the DFS Webpage and are attached to FMD 143.

6.6.3 ORA Technical Accomplishment Report

An ORA Technical Accomplishment Report, prepared by the Science Advisor Working Group (SAWG), will be published annually for all projects completed in the preceding year. The quarterly research project summary spreadsheets, progress reports, and impact reports are used to compile this report on completed projects with attention to both achievements and areas of concern. The purpose of this report is to assist both the Laboratory Directors and ORA with future research planning.

The SAWG will also prepare periodic follow-up reports on research to include regulatory impact, publications, presentations, collaborative studies, adoption as official methods (adoption by other field and headquarters laboratories), inclusion in compliance programs, and etc.

6.6.4 Time Reporting

Reporting requirements for district discretionary research are established by local management. Any research that exceeds 80 hours can be reported to DFS for issuance of an RPN tracking number. Impact reports for district discretionary research can be submitted when appropriate. Resources used to accomplish all types of field research must be reported into FACTS.

6.7 Research Products

The basic product of scientific research is information. Dissemination of that information is necessary to ensure that others interested in the problem can use the data. To accomplish this, ORA encourages and supports several types of research products.

6.7.1 Publications

Research results may be published for internal distribution, e.g., *Laboratory Information Bulletins* (LIB), or as articles in outside publications. In either case, the manuscript must be cleared for publication according to Field Management Directive No. 66. Manuscripts for outside publications must be reviewed and approved for technical correctness by the regional management or their designees before submission to the editor of the publication. Local management is responsible for funding and ordering reprints. Manuscripts intended for publication as an LIB must be reviewed and approved by the Science Advisor, Laboratory Director, and District Director before submission to DFS.

6.7.2 Presentations

Research results may be presented at scientific meetings as lectures or audio-visual sessions. Clearance of the presentations is the responsibility of regional management or their designees.

6.7.3 Collaborative Studies

After the study initiator has performed ruggedness testing and/or intra-laboratory collaboration to ensure that a method is likely to succeed in a full-scale study, a request, accompanied by the method and collaborative study protocol, is sent to DFS to select collaborators for the study. DFS will review the proposed study for suitability of the method and clarity of the directions as stated in the protocol. DFS issues the call for collaborators and informs the initiator of those who agree to participate. In an AOAC collaborative procedure, the initiator must obtain approval from local management before requesting Associate Referee status from the appropriate AOAC General Referee.